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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,625	04/20/2005	Nava Zisapel	2007-120	9296

6449 7590 12/09/2010

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EXAMINER	
TOWNSLEY, SARA ELIZABETH	
ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
12/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/510,625	ZISAPEL, NAVA	
	Examiner	Art Unit	
	SARA E. CLARK	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-37,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-37, 48, and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 9/30/2010.

Claims 1-28 and 38-47 have been cancelled.

Claim 29 has been amended.

No new claims have been added.

Thus, claims 29-37, 48, and 49 now represent all claims currently pending and under consideration.

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/19/2010 has been entered.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted.

WITHDRAWN REJECTIONS

Rejections under 35 USC §103

Due to the amendments to the claims, the rejection of claims 29-31, 34-37, 48, and 49 under 35 USC 103 as obvious over Suhner (Aviation, Space and Environmental Medicine Vol. 72, 638-646 (2001) in view of Ohkawa (USPN 6,348,485) is withdrawn.

Due to the amendments to the claims, the rejection of claims 32 and 33 under 35 USC 103 as obvious over Suhner and Ohkawa, further in view of Richardson (USPN 6,042,849) is withdrawn.

Due to the amendments to the claims, the rejection of claims 29-31, 34-37, 48, and 49 under 35 USC 103 as obvious over Ohkawa (USPN 6,348,485) is withdrawn.

Due to the amendments to the claims, the rejection of claims 32 and 33 under 35 USC 103 as obvious over Ohkawa further in view of Richardson, is withdrawn.

NEW REJECTIONS

Claim Rejections - 35 USC § 112, First Paragraph

New Matter

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 29-37, 48, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Specifically, amended claim 29 is drawn to a method of promoting sleep initiation for a human who has difficulty falling asleep comprising administering a sustained-release form of melatonin in combination with at least one non-barbiturate, non-benzodiazepine hypnotic compound, wherein the amount of melatonin is effective to potentiate the compound's hypnotic effect and enhance said human's daytime vigilance.

The disclosure does not support the limitation "enhancing said human's daytime vigilance" upon administration of sustained-release melatonin in combination with the claimed hypnotic compounds. The specification (Example 2) describes that somnolence (drowsiness) is the most common treatment-emergent adverse event observed upon the administration of zolpidem alone, melatonin alone, and zolpidem + melatonin in combination; in particular, "[t]he incidence of somnolence was similar with zolpidem and zolpidem + sustained-release melatonin, but had clearly increased compared with melatonin alone and placebo" (p. 12, last para.). Thus, while sustained-release melatonin alone improves daytime vigilance (see also spec. p. 13, third full para.), the specification discloses that the claimed combination results in *reduced*, not *enhanced*, daytime vigilance, as compared to melatonin alone and control.

Further, Examples 4 and 5 disclose enhanced daytime vigilance following the administration of melatonin alone, but not in combination with a hypnotic compound; and Example 7 discloses the administration of melatonin in combination with zolpidem, but no information or data is provided as to daytime vigilance. In addition, the specification discloses that "[n]o hypnotic drug has ever been shown to increase daytime vigilance" (p. 15, last para). Further, if the amount of melatonin is effective to potentiate the compound's hypnotic effect, as recited by claim 29, a further decrease in daytime vigilance would reasonably be expected.

Therefore, a recitation limiting the scope of the claims to methods of administering melatonin in combination with a hypnotic compound "wherein the amount of melatonin is effective to . . . enhance said human's daytime vigilance" encompasses subject matter which is directly contradicted by the specification. See MPEP §706.03(o).

Enablement

3. Claims 29-37, 48, and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for methods of promoting sleep initiation for a human who has difficulty falling asleep comprising administering a sustained-release form of melatonin in combination with at least one non-barbiturate, non-benzodiazepine hypnotic compound, wherein the amount of melatonin is effective to potentiate the compound's hypnotic effect, wherein the human's daytime vigilance is enhanced. The specification does not enable a person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to practice

the invention commensurate with the scope of these claims. MPEP 2164.01(a), citing *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), sets out the factors to determine whether experimentation is undue, which include:

(A) The nature of the invention and the breadth of the claims. The claims are drawn to methods of promoting sleep initiation for a human who has difficulty falling asleep comprising administering a sustained-release form of melatonin in combination with at least one non-barbiturate, non-benzodiazepine hypnotic compound, wherein the amount of melatonin is effective to potentiate the compound's hypnotic effect *and enhance said human's daytime vigilance*. The dependent claims limit these methods by specifying how the two active agents are formulated (claims 30-33); the hypnotic compound zolpidem (claims 34-37 and 48); and the amount of hypnotic compound in a sub-therapeutic dose (claims 31 and 49).

Thus, the claimed compounds and method steps are not unreasonably broad or unsupported by the disclosure. However, methods which result in *enhanced daytime vigilance* following administration of the claimed compounds are contradicted by the disclosure and contrary to what was known in the art.

(B) The state of the prior art and the level of predictability in the art. Suhner (2001, cited in the previous Action) discloses methods of promoting sleep onset and treating jet-lag by administering melatonin alone, zolpidem alone; and melatonin + zolpidem; in-flight to eastbound transcontinental passengers crossing six to nine time zones, during a specified interval of time during the flight and on each of the next 4 nights after arrival (p. 639, col.. 2, para 1). The results are compared and the advantages and

disadvantages of each formulation are analyzed (tables I-III and figs. 1-3). A number of data points over the five treatment days suggests that melatonin may well have a potentiating effect on the hypnotic compound in the melatonin + zolpidem cohort versus the zolpidem-alone cohort, in particular the data relating to sleep latency on night 3 and wakeful periods after sleep onset on days 1, 2 and 4 (p. 642, table II), which can be considered measures of hypnotic effect.

However, Suhner also discloses that "[t]hose taking the combination zolpidem/melatonin found it more difficult to wake up and become fully alert in the morning as compared with the other groups, whereas those taking placebo had the least problems in this regard" (p. 641, left col.). "Enhanced daytime vigilance" is not defined by the specification, but is reasonably construed to encompass ease in waking up and/or becoming fully alert in the morning. Thus, the greater difficulty waking up and achieving full alertness in the morning observed in the melatonin + zolpidem cohort as compared to a control group is interpreted as *reduced* daytime vigilance upon administration of melatonin + zolpidem.

It is noted that the data disclosed by Suhner relates to the administration of regular-release melatonin, rather than sustained-release melatonin, as recited by claim 29. Nonetheless, the data presented by Suhner would reasonably suggest to a skilled artisan that administering the hypnotic compound zolpidem in combination with melatonin, in any form, would be unlikely to result in enhanced daytime vigilance. It is noted that the Applicant agrees: "[o]ne of skill in the art reading the Suhner paper would not have any reason to believe that the administration of a hypnotic compound and

sustained release melatonin could have such effects [enhanced vigilance the next day] (Remarks dated 9/30/2010, p. 6). This conclusion is also reinforced by the instant specification, as described below.

(C) The amount of direction provided and/or the existence of working examples.

The disclosure contradicts the limitation "enhancing said human's daytime vigilance" upon administration of sustained-release melatonin in combination with zolpidem. The specification (Example 2) describes that somnolence (drowsiness) is the most common treatment-emergent adverse event observed upon the administration of zolpidem alone, melatonin alone, and zolpidem + melatonin in combination; in particular, "[t]he incidence of somnolence was similar with zolpidem and zolpidem + sustained-release melatonin, but had clearly increased compared with melatonin alone and placebo" (p. 12, last para.). Thus, while sustained-release melatonin alone improves daytime vigilance (spec. p. 13, third full para.), the specification discloses that the claimed combination results in *reduced*, not *enhanced*, daytime vigilance, as compared to melatonin alone and control.

Further, Examples 4 and 5 disclose enhanced daytime vigilance following the administration of melatonin alone, but not in combination with a hypnotic compound; and Example 7 discloses the administration of melatonin in combination with zolpidem, but no information or data is provided as to daytime vigilance. In addition, the specification discloses that "[n]o hypnotic drug has ever been shown to increase daytime vigilance" (p. 15, last para). Further, if the amount of melatonin administered is

effective to potentiate the compound's hypnotic effect, as recited by claim 29, a further decrease in daytime vigilance would reasonably be expected.

(D) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Because the pharmaceutical arts are generally unpredictable, it requires each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F 2d. 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is needed in order to satisfy the statute. Here, the instantly claimed invention is highly unpredictable because a skilled artisan would reasonably doubt that administration of the claimed combination of melatonin and a hypnotic compound would result in *enhanced* daytime vigilance; rather, *reduced* daytime vigilance would be expected, as disclosed by the prior art and the specification. Thus, undue experimentation would be required to practice the claimed invention with a reasonable expectation of success.

CONCLUSION

Claims 29-37, 48, and 49 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Fri, 8:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon, can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1613

/Barbara P. Badio/
Primary Examiner, Art Unit 1628